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KDIGO executive conclusions

Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis

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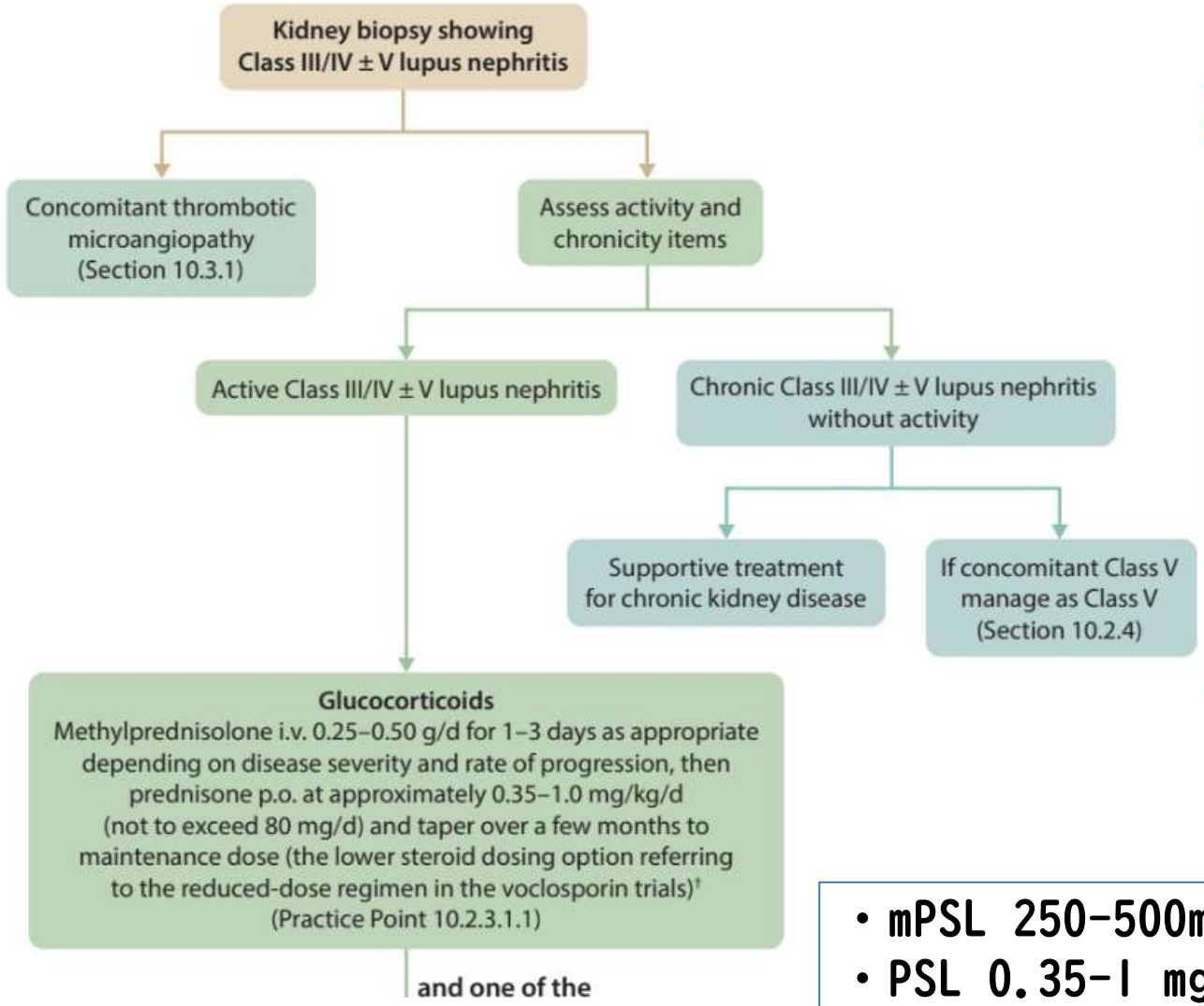
Brad H. Rovin[1], Isabelle M. Ayoub[1], Tak Mao Chan[2], Zhi-Hong Liu[3], Juan M. Mejía-Vilet[4], Ethan M. Balk[5], Craig E. Gordon[6], Gaelen Adam[5], Marcello A. Tonelli[7], Michael Cheung[8], Amy Earley[8] and Jürgen Floege[9]

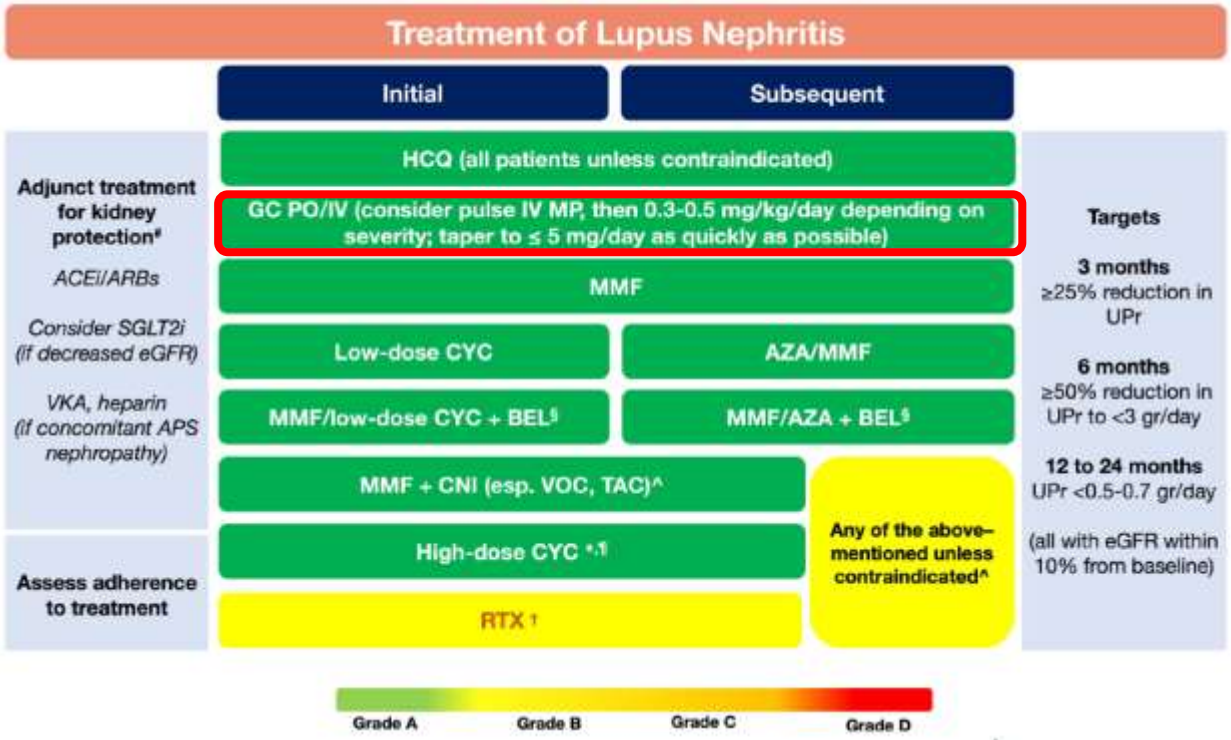
KDIGO: The Kidney Disease: Improving Global Outcomes

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseasesのアップデート版
具体的にはBelimumabとVoclosporinがLNに対してFDA及びEMAにて承認されたことを受けた改訂

Fig. 1(前半)　　LN III/IV型の寛解導入療法



＜参考＞Eular 2023 update



- mPSL 250-500mg/d x 1-3 days
- PSL 0.35-1 mg/kg/d (max 80mg/d)
- 数カ月で維持量まで減量
  （減量方法は後述）

＜参考＞Eular/ERA-EDTA 2019

mPSL pulse（計0.5-2.5g）
その後PSL 0.3-0.5mg/kg/日を4週間
3-6ヶ月以内にPSL 7.5mg/日以下へ

グルココルチコイドの減量方法の例

Practice Point 10.2.3.1.1: A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement (Figure 7).

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Figure 7 | Examples of glucocorticoid regimens for lupus nephritis.

どのレジメンでも6ヶ月でPSL 5mg/日未満へ

＜参考＞ voclosporin AURORA I studyにおけるGCの減量法

Figure S1 Phase 3 AURORA 1 clinical trial study design

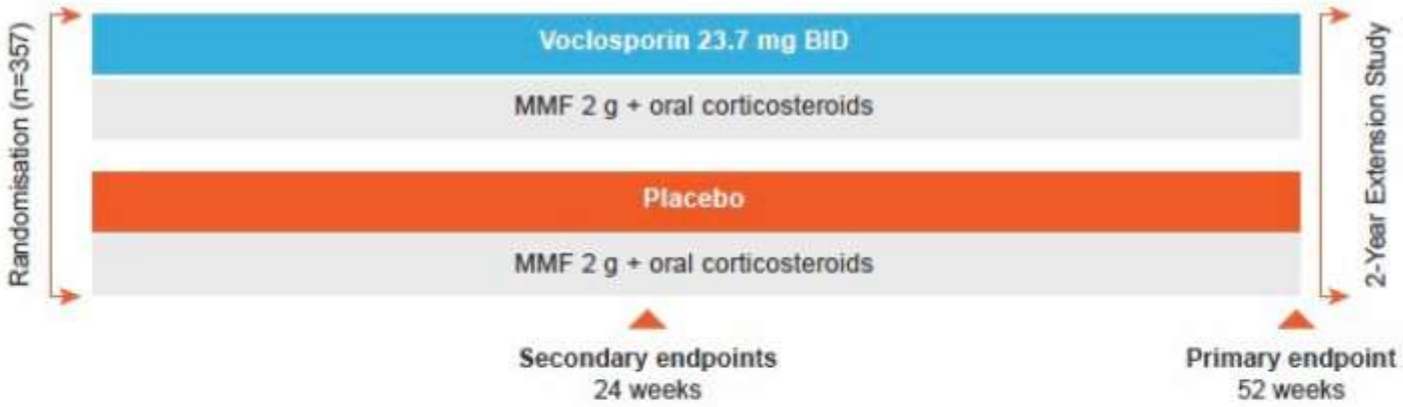
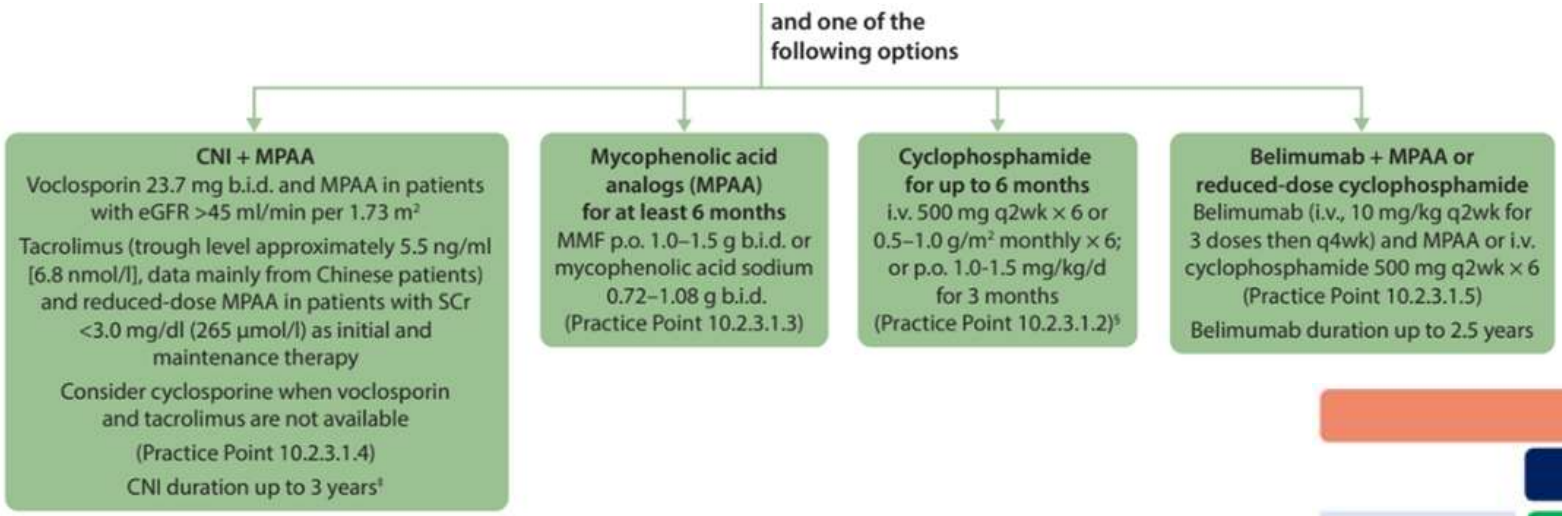


Table S3 Dosing Schedule for IV Methylprednisolone and Daily Oral Prednisone

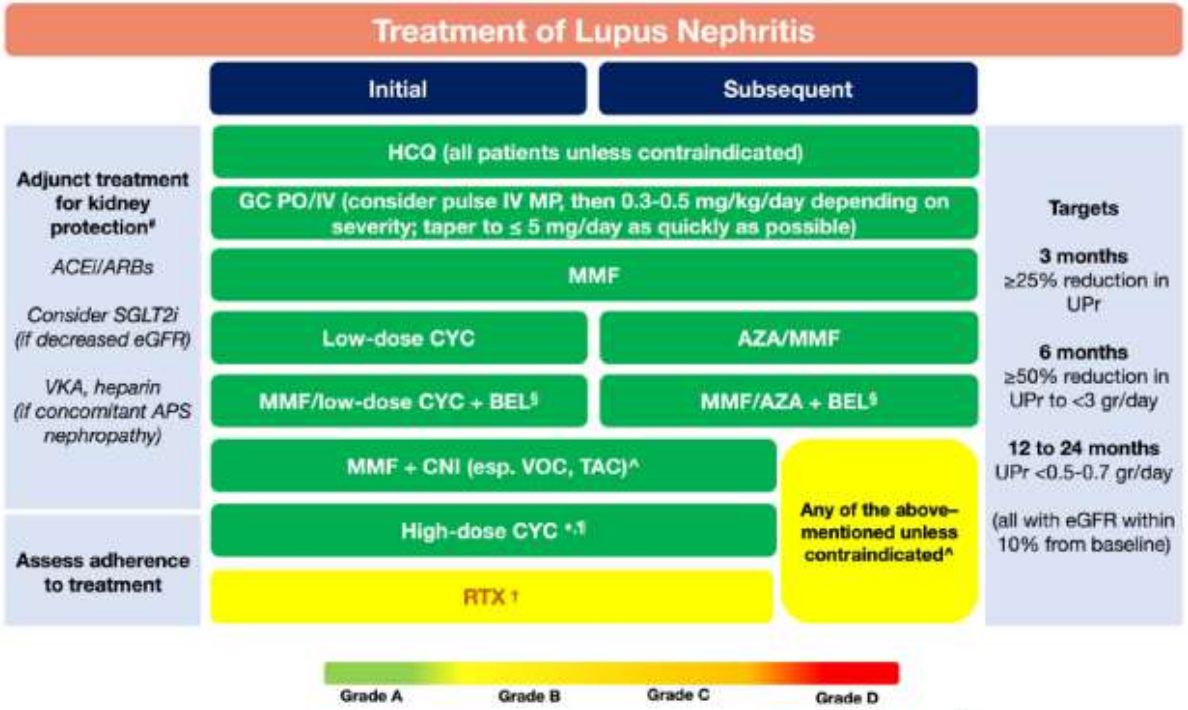
	Patients <45 kg	Patients ≥45 kg	In Case of Prior IV Steroids During Screening (pre-randomisation)
Weeks 1-2*	0·25 g (IV)	0·5 g (IV)	1 g minus prior IV steroids mg or 0·5 g minus prior IV steroids mg for patients who weigh <45 kg‡
Days 1-2†			
Days 3-13	20 mg (oral)	25 mg (oral)	
Week 2 (Day 14)	15 mg (oral)	20 mg (oral)	
Week 4 (Day 28)	10 mg (oral)	15 mg (oral)	
Week 6 (Day 42)	10 mg (oral)	10 mg (oral)	
Week 8 (Day 56)	5 mg (oral)	5 mg (oral)	
Week 12 (Day 84)	5 mg (oral)	5 mg (oral)	
Week 16 (Day 112)	2·5 mg (oral)	2·5 mg (oral)	

Fig. 1(後半)　LN III/IV型の寛解導入療法



PSL＋４つのIS治療のうちのいずれか
（cost、availability、妊孕性、CKDなどを考慮）
・MMF + CNI（Voc or Tac or CyA）
　eGFR>45の患者対象　CNIは3年まで(*)
・MMF単剤（最低6ヶ月）
・IVCY or POCY（3-6ヶ月）
・MMF + BEL or IVCY（BELは2.5年まで(*)）
(*) clinical trialにおいて腎機能含めた副作用が悪化しなかったと証明されている期間

＜参考＞Eular 2023 update



＜参考＞Eular/ERA-EDTA 2019

MMF or IVCY（Low dose）を併用
MMF+CNIはネフローゼには推奨
IVCY（high dose）も重症例には考慮

Triple therapy時におけるCNIとBELの使い分けのポイント

Table 1 | Factors to consider when using United States Food and Drug Administration (FDA)–approved drugs in lupus nephritis

Clinical attributes	Voclosporin	Belimumab
Kidney function	Use cautiously if GFR is impaired (e.g., <45 ml/min per 1.73 m^2)	May be used if GFR is at least 30 ml/min per 1.73 m^2; may slow decline of GFR[a]
Kidney histology	Use cautiously if widespread sclerotic and/or fibrotic changes are present	Not determined
Proteinuria	Effective at any level of proteinuria; may be especially effective in patients with severe proteinuria with significant podocyte damage	More effective in patients with proteinuria <3 g/d
High risk of disease flare	No effect on flare rate	May decrease rate of severe flares
Background immunosuppression	Was not tested in combination with cyclophosphamide	Effective in combination with MMF; uncertain effectiveness in combination with cyclophosphamide
Need for parenteral therapy	Oral only	Intravenous/subcutaneous
Significant extrarenal lupus	Efficacy in extrarenal lupus to be determined	Long track record of efficacy in extrarenal lupus
Safety	Add-on therapy did not increase the incidence of adverse events; monitor acute eGFR variations with voclosporin	Add-on therapy did not increase the incidence of adverse events
Pregnancy	Use not recommended (consider tacrolimus)	Use not recommended

GFR, glomerular filtration rate; MMF, mycophenolate mofetil.
[a]In patients with advanced chronic kidney disease, the benefit of any immunosuppression should be carefully weighed against the likelihood of harm.

Pure Class Vの治療方法（基本的に変わりなし）

10.2.4 Class V lupus nephritis

Practice Point 10.2.4.1: A suggested approach to the management of patients with pure Class V LN is described in Figure 10.

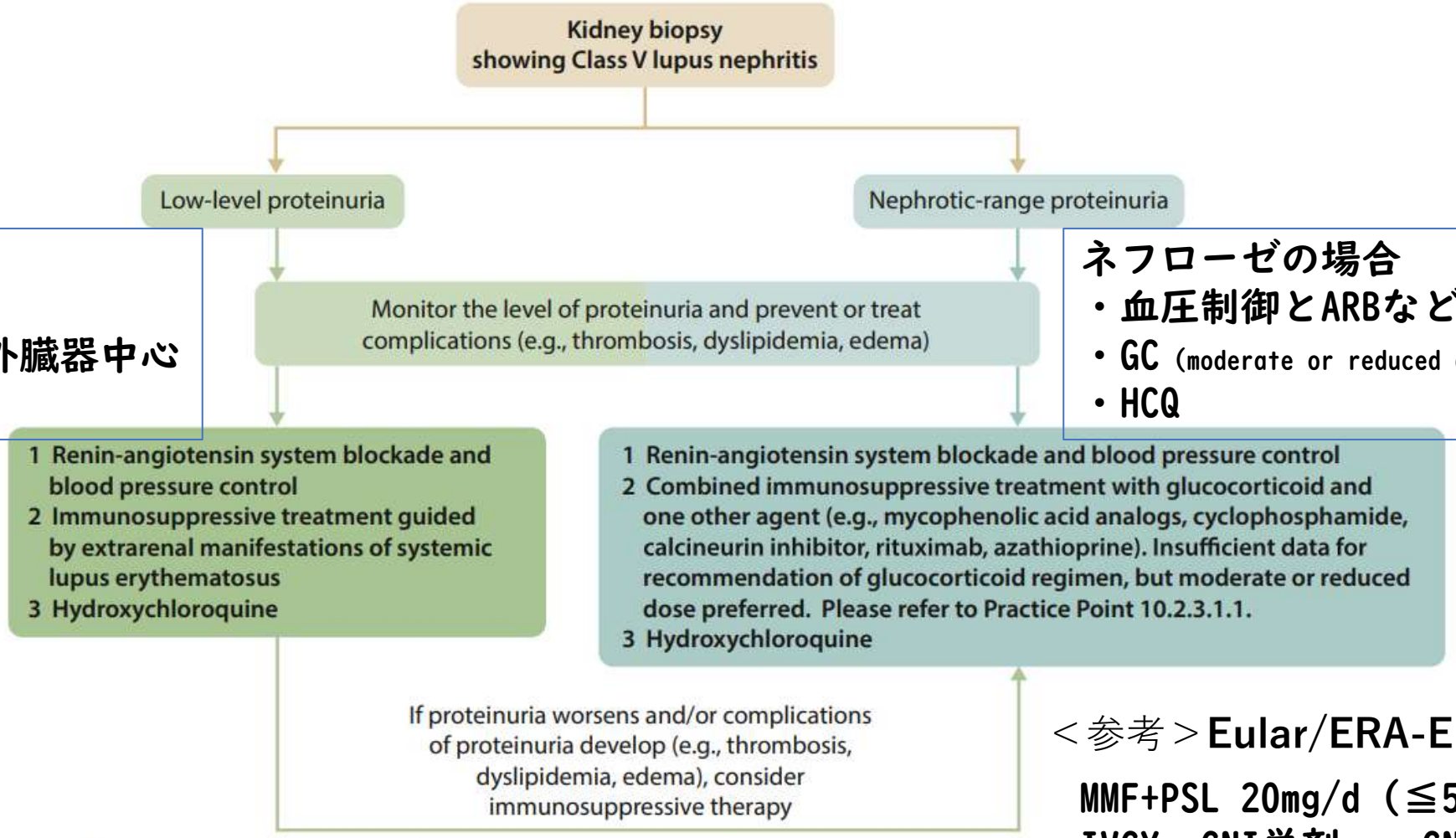


Figure 10 | Management of patients with pure Class V lupus nephritis.

低蛋白尿の場合
- 血圧制御とARBなど
- 免疫抑制療法は腎以外臓器中心
- HCQ

ネフローゼの場合
- 血圧制御とARBなど
- GC (moderate or reduced dose)+IS1剤
- HCQ

＜参考＞Eular/ERA-EDTA 2019

MMF+PSL 20mg/d（≦5mg/d/3Mへ）
IVCY，CNI単剤 or CNI+MMFもあり
HCQ

Class III/IVの維持療法（PSL<5mg/d）

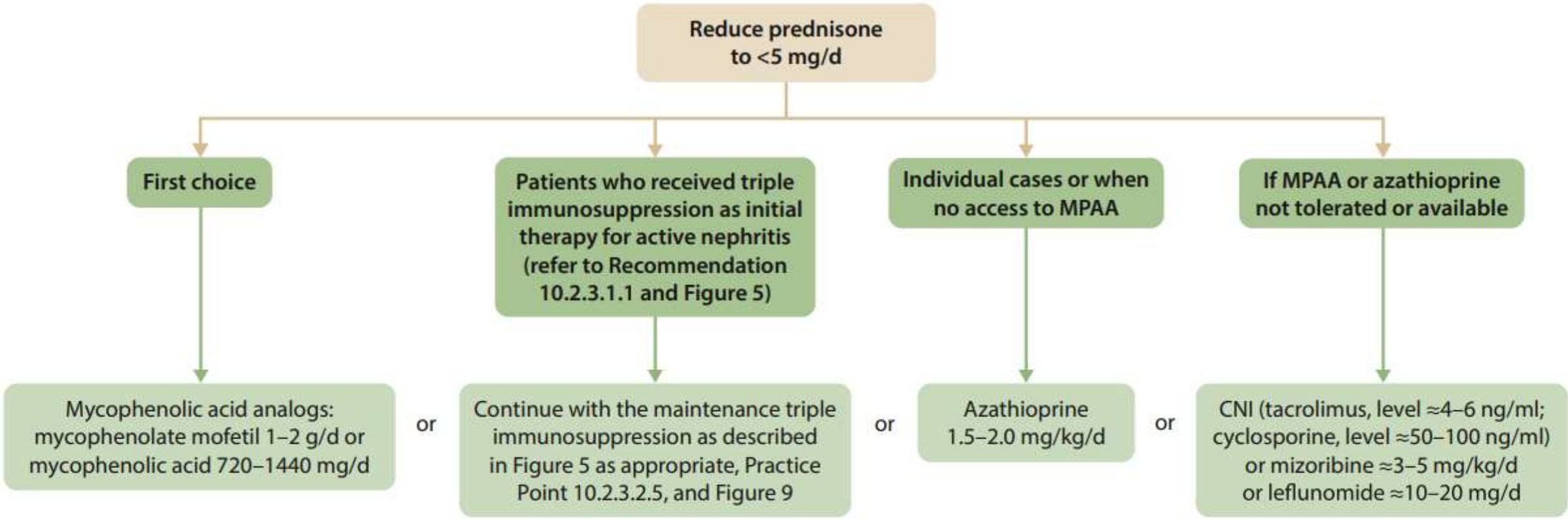
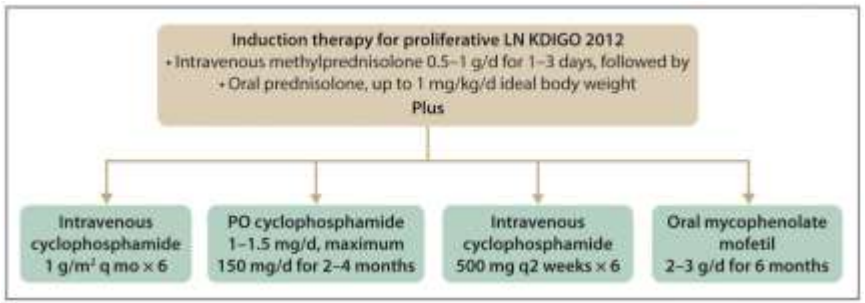
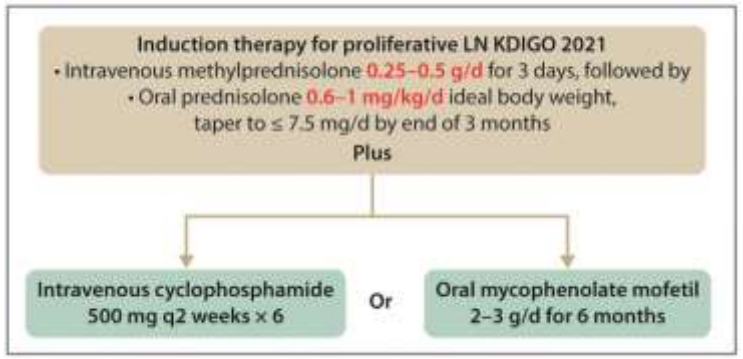
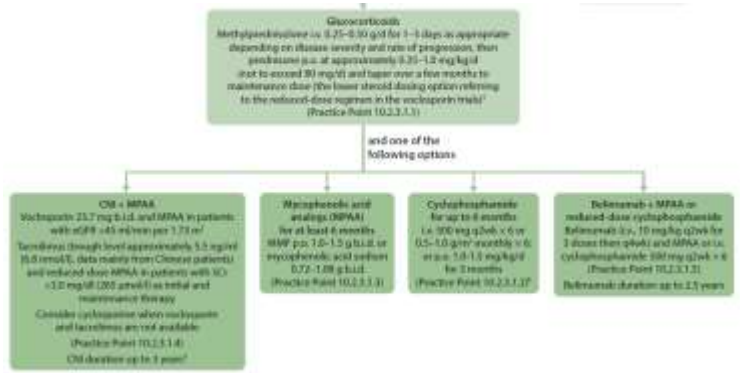


Figure 8| Recommended options of maintenance therapy for Class III and Class IV lupus nephritis. The target ranges of calcineurin inhibitors (CNIs) have been based on the transplant literature. The Kidney Disease: Improving Global Outcomes (KDIGO) Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine level, reducing the dose if the serum creatinine level increases but does not plateau or increases to over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. MPAA, mycophenolic acid analogs.

＜参考＞ KDIGO 2012, 2021, 2024の比較 寛解導入 class III/IV







KDIGO	2012	2021	2024
mPSL pulse	0.5-1g/d x 1-3d	0.25-0.5g/d x 3d	0.25-0.5g/d x 1-3d
PSL	～1mg/kg/d	0.6-1mg/kg/d	0.35-1mg/kg/d
PSL taper		7.5mg/d by 3M	３つのプロトコール（Hi 15mg/3M, 5mg/6M; Mod 10mg/3M, <5mg/6M Lo 5mg/3M, 2.5mg/6M）
免疫抑制薬	IVCY Hi or Lo POCY MMF	IVCY Lo MMF	CNI + MPAA（日本はMMFのみ） MPAA IVCY Lo, Hi or POCY BEL + MPAA or IVCY Lo

＜参考＞　KDIGO 2012，2021，2024の比較 維持療法

12.4: Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Maintenance Therapy

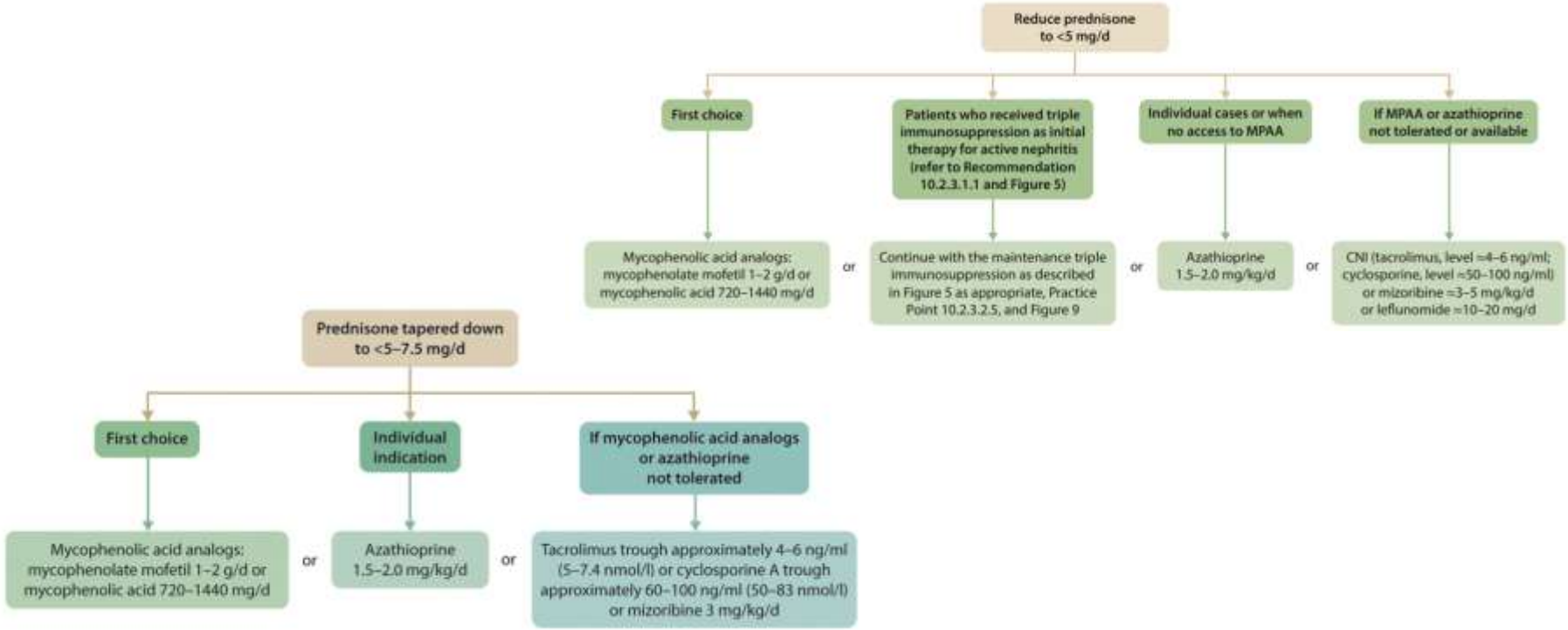
12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5-2.5 mg/kg/d) or MMF (1-2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (*1B*)

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)



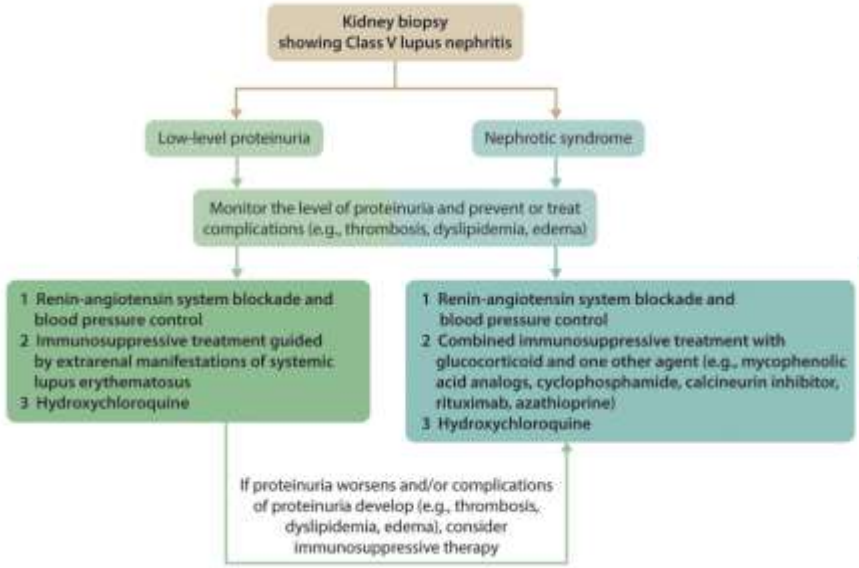
KDIGO	2012	2021	2024
維持療法 PSL	≦10mg/d	<5-7.5mg/d	<5mg/d
維持療法 IS	AZA or MMF	MPAA (1st)	MPAA (1st)
	CNI (MMF使用困難例)	AZA (2nd)	Triple Therapy (Triple開始症例)
		CNI or MZB (3rd)	AZA (MMF使用困難例)
			CNI or MZB or LEF (MPAA/AZA使用困難例)

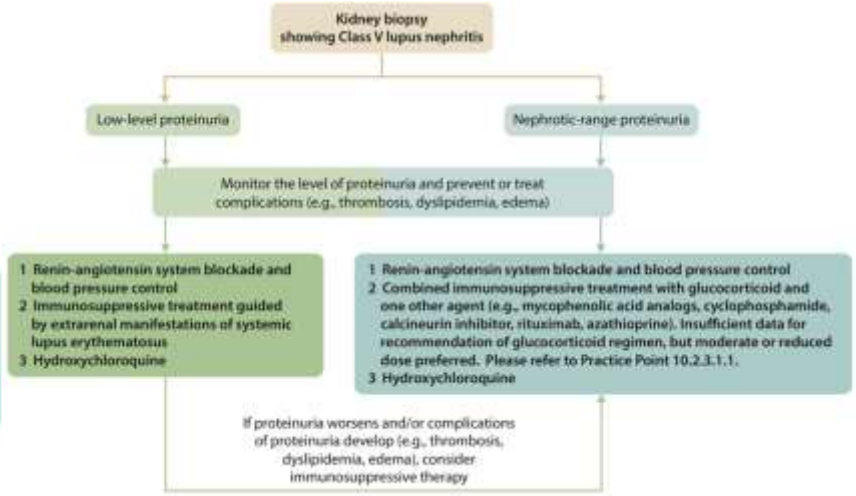
＜参考＞ KDIGO 2012, 2021, 2024の比較 pure class V

12.5: Class V LN (Membranous LN)

12.5.1: We recommend that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).





KDIGO	2012	2021	2024
低尿蛋白	RAS阻害 & 降圧薬 GC/ISは他臓器で必要時	RAS阻害 & 降圧薬 GC/ISは他臓器で必要時 HCQ	RAS阻害 & 降圧薬 GC/ISは他臓器で必要時 HCQ
ネフローゼ	GC + one IS (CY/CNI/MMF/AZA)	GC + one IS + HCQ (MFAA/CY/CNI/RTX/AZA)	GC + one IS + HCQ (MFAA/CY/CNI/RTX/AZA)

まとめ

- KDIGO 2024 LN guidelineの改訂ポイントはBELとVOCの位置づけを行った点
- GC減量プロトコールの例を挙げた点は大きい
- LN class III/IVの治療において、EULAR recommendations 2023と基本的には変わらない
- LN Class V治療はevidence少なく改訂ほぼなし。EULAR 2023ではclass III/IVとVをわけずに推奨している。